Inflammation, Vol. 35, No. 4, August 2012 (© 2012)
DOI: 10.1007/s10753-012-9445-6

Chronic Inflammation Is Correlated with Percentage of Body Fat Independent of the Burden of Infection

Katayoun Vahdat,[1] Fatemeh Azizi,[1] Keivan Zandi,[1] Majid Assadi,[2] and Iraj Nabipour[3,4]

Abstract—The aim of this population-based study was to investigate the association of the percentage of body fat (BF) and high-sensitivity C-reactive protein (hs-CRP) when the infectious burden was adjusted for. A total of 1,546 subjects were randomly selected. BF was determined using bioelectrical impedance analysis. Sera were analyzed for IgG antibodies to *Chlamydia pneumoniae*, herpes simplex virus type 1, *Helicobacter pylori*, and cytomegalovirus using ELISA. Measurement of C-reactive protein (CRP) by a high-sensitivity CRP assay was performed. A linear relationship between an increase in the number of pathogens and CRP concentrations was observed (p=0.007). Age-adjusted serum hs-CRP levels were correlated with percentage of BF in men (r=0.28, p<0.0001) and women (r=0.37, p<0.0001). In multiple regression analyses, hs-CRP showed significant correlations with percentage of BF after controlling for age, sex, cardiovascular risk factors, and the infectious burden was divided into two, three, and four pathogens [(β=0.24, p<0.0001), (β=0.2 1, p<0.0001), and (β=0.23, p=<0.0001), respectively]. In conclusion, there was a strong association between hs-CRP and percentage of body fat independent of viral and bacterial pathogens that had been previously associated with coronary artery disease as well as carotid atherosclerosis.

KEY WORDS: obesity; body fat; C-reactive protein; burden of infection; adipose tissue.

INTRODUCTION

Recent research has pinpointed adipose tissue as an active organ in modulating glucose and energy metabolism, insulin sensitivity, bone metabolism, immunity, and inflammation. This dynamic endocrine tissue produces a variety of proinflammatory and anti-inflammatory molecules, including leptin, adiponectin, resistin, visfatin, monocyte chemoattractant protein 1 as well as cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 [1].

It has been proposed that adipose tissue-derived proinflammatory cytokines contribute to the progression of multiple cardiometabolic risk factors independently of the body mass index (BMI) through production of chronic low-grade inflammation [2, 3]. Numerous studies in various parts of the world have clearly established that the C-reactive protein (CRP), as a blood biomarker for low-grade inflammation, predicts myocardial infarction, coronary artery disease death, stroke, peripheral artery disease, sudden death, *etc*. [4]. Thus, the Centers for Disease Control and the American Heart Association have issued a statement recommending that patients at intermediate risk of coronary artery disease might benefit from measurement of CRP [5].

The direct association between adiposity and low-grade inflammation has been under close investigation in both cross-sectional [6, 7] and longitudinal studies [8, 9]. In the medical literature, the correlation between subcutaneous and visceral adipose tissue and markers of chronic low-grade inflammation, in particular the presence of the highly sensitive C-reactive protein (hs-CRP), is well described [10–13]. Visceral fat thickness was reported to be the strongest contributor to circulating hs-CRP in

[1] Department of Infectious Diseases, The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran
[2] The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran
[3] Department of Biochemistry, The Persian Gulf Marine Biotechnology Research Center, Bushehr University of Medical Sciences, Boostan 19 Alley, Imam Khomeini St, Bushehr, IR, Iran 7514763448
[4] To whom correspondence should be addressed at Department of Biochemistry, The Persian Gulf Marine Biotechnology Research Center, Bushehr University of Medical Sciences, Boostan 19 Alley, Imam Khomeini St, Bushehr, IR, Iran 7514763448. E-mail: inabipour@gmail.com

patients with vascular diseases [13]. Although little is known about the biologic mechanisms that underlie this association, circulating hs-CRP was proposed as a biomarker of the presence of dysfunctional adipose tissue that handles the positive energy balance poorly [14]. In contrast, adiposity, particularly visceral adipose tissue, was suggested as a key promoter of low-grade chronic inflammation [10].

Chronic viral and bacterial infections induce the production of various proinflammatory cytokines, such as TNF-α and IL-6, which lead to chronic low-grade inflammation [15–17]. Although little is known about the correlation between measures of obesity and chronic viral and bacterial infections, the burden of infection could be simultaneously involved with chronic low-grade inflammation and obesity [18, 19]. The burden of infection is defined as the aggregate number of seropositivities of infectious pathogens to which an individual has been exposed [20].

Both adiposity and chronic viral and bacterial infections are sources of inflammatory stimuli and can amplify inflammatory mediators, resulting in upregulating inflammatory pathways and hs-CRP production. However, whether the presence of chronic subclinical infections with bacterial or viral pathogens influences the relationship between hs-CRP and adiposity has not yet been well established. However, this knowledge might provide useful insight into the pathophysiology of obesity, chronic inflammation, and atherosclerosis. Therefore, in a large community-based study of an Iranian population, we investigated the association of the percentage of body fat (BF) as a measure of adiposity and circulating levels of hs-CRP when the infectious burden was adjusted for in logistic regression models.

MATERIALS AND METHODS

Community Sampling

We conducted the present study as part of the Persian Gulf Healthy Heart Study, which was a prospective population-based cohort study begun in 2003–2004 and based on men and women subjects aged >=25 years. The Persian Gulf Healthy Heart Study was designed to determine the risk factors for cardiovascular diseases among the northern Persian Gulf population (Bushehr and Hormozghan Provinces) and to develop community-based interventional projects to change the lifestyles of the population and to present the rising threat of cardiovascular diseases in the region. The design of the present study encompasses two major components: phase I is a cross-sectional prevalence study of unhealthy lifestyles, ischemic heart disease, and associated risk factors, and phase II is a multiple interventional project for the reduction of cardiovascular diseases in the region.

In the present study, which is ancillary to the Persian Gulf Healthy Heart Study, 1,546 (49.3% males and 50.7% females) subjects were selected through a stratified multistage design from the major ports of Bushehr Province (an Iranian province having the longest border on the Persian Gulf).

A fasting blood sample was taken, and all samples were promptly centrifuged and separated. Analyses were carried out at the Persian Gulf Health Research Center on the day of blood collection, using a Selectra 2 autoanalyzer. Detailed information about the methods and procedures of this study is available elsewhere [21].

Examinations

Blood pressure was assessed twice at the right arm after a 15-min rest in the sitting position, using a standard mercury sphygmomanometer. Height and weight were measured using a stadiometer. Heavy outer garments and shoes were removed before measuring height and weight. Waist circumference was defined at the midway level between the costal margins and the iliac crests. Hip circumference was measured at the level of the greater trochanters. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Percentage of body fat was determined using bioelectrical impedance analysis with the portable apparatus (OMRON BF 302, OMRON Matsusaka Co., Ltd. Japan) with accuracy up to 0.1%. Lukaki *et al*. presented the basic principles of bioelectric impedance analysis [22].The OMRON body fat monitor has been validated [23].

Definitions

Using American Diabetes Association criteria, a fasting plasma glucose of 126 mg/dL or greater or the use of antidiabetic measures was defined as diabetes [24]. The cutoff points of serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) distributions used to assign subjects to different levels of risk were those derived from the National Cholesterol Education Program guidelines in the USA (Adult Treatment Panel III) [25]. A subject was considered hypertensive if the blood pressure was at least 140/90 mmHg. Respondents were

classified as active if they reported sufficient physical activity of moderate intensity (≥30 min per day ≥5 days per week) or of vigorous intensity (≥20 min per day ≥3 days per week). Smoking was considered to be present when the participant smoked cigarettes or used a shisha (water pipe) daily. The aggregate number of seropositivities to *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus (CMV), or herpes simplex virus type 1 (HSV) was defined as a pathogen burden [20].

Serology

IgG antibodies against *C. pneumoniae* were measured by a commercial test kit (DRG Instruments GmbH, Germany). The principle of the kit was based on an indirect solid-phase enzyme immunoassay with horseradish peroxidase as a marker enzyme; the positivity threshold was enzyme immunounits >45. Sera were screened for IgG antibodies against HSV, CMV, and *H. pylori* with an ELISA kit (Radim SpA, Italy), and the samples were considered positive with IgG values higher than 30 RU/ml for CMV and *H. pylori*. Samples with optical density higher than the cutoff control were considered reactive for anti-HSV type 1 IgG antibodies. Measurement of CRP was performed by a high-sensitivity CRP assay, CRP HS ELISA (DRG International, Inc. USA). The minimum detectable concentration of the CRP HS ELISA assay was estimated to be 0.1 mg/l. Additionally, the functional sensitivity was determined to be 0.1 mg/l (as determined by inter-assay % CV <20%).

Statistical Analysis

Normal distribution of the data was controlled with the Kolmogorov–Smirnov test. Probability values <5% were considered statistically significant. The significance of the difference in the results of any two groups was determined by chi-square analysis using 2×2 contingency tables for categorical variables and ANOVA for continuous variables. A two-tailed *t* test was used to compare the mean values across groups. A $p<0.05$ was considered statistically significant. We found that log transformation of hs-CRP gave a better fit to a Gaussian distribution. The geometric mean for CRP was defined as the arithmetic mean of the log-transformed data±2 SD raised to the power of 10. Multiple linear regression models were used to assess the association between percentage of BF, waist circumference, and waist-to-hip ratio (independent variables) and hs-CRP levels (dependent variable); each independent variable was considered a separate independent variable in a series of models. Age, smoking, physical inactivity, dyslipidemia, hypertension, diabetes mellitus, and pathogen burden (four, three, two pathogens *versus* zero to one pathogen) were considered covariates in multiple linear regression models.

We excluded 187 subjects with hs-CRP concentrations >=10.0 mg/l from statistical analysis to omit possible cases of acute infections and other occult diseases.

All statistical analyses were performed using the PASW Statistics GradPack 18 (SPSS Inc., Chicago, IL).

RESULTS

A total of 1,546 (49.3% males and 50.7% females) subjects were evaluated for the association of percentage of BF and hs-CRP levels. Of the studied subjects, 40.7% were between 25 and 34 years, 29.3% between 35 and 44 years, 19.2% between 45 and 54 years, and 10.8% between 55 and 66 years. The prevalence of the consumption of antihypertensive, hypolipidemic, and antidiabetic drugs was 5.2%, 3.5%, and 3.8%, respectively. Of the studied population, 24.1%, 48.5%, 19.2%, 20.5%, and 7.1% had hypertension, low HDL-C, high LDL-C, hypercholesterolemia, and diabetes mellitus, respectively.

The baseline characteristics including anthropometric information, cardiovascular risk factors, and the prevalence of IgG antibodies against CMV, HSV, *C. pneumoniae*, and *H. pylori* in men and women are presented in Table 1. Women had higher percentages of BF, BMI, waist circumference, and hs-CRP levels than men ($p<0.0001$). Women also had significantly higher seropositivity for CMV and *H. pylori* but lower seropositivity for *C. pneumoniae* than men (Table 1).

The prevalence of IgG antibodies against CMV, HSV, *C. pneumoniae*, and *H. pylori* was 93.3%, 85.6%, 40.7%, and 61.3%, respectively. The prevalence of the number of pathogens (zero to one, two, three, and four) was 6.8%, 26.7%, 42.6%, and 23.8%, respectively.

The geometric mean levels of hs-CRP across quartiles of percentages of BF for men and women are shown in Figs. 1 and 2. Age-adjusted serum hs-CRP levels were correlated with percentage of BF in men ($r=0.28$, $p<0.0001$) and women ($r=0.37$, $p<0.0001$). Likewise, age-adjusted circulating hs-CRP levels were correlated with waist circumference ($r=26$, $p<0.0001$ for men and $r=0.38$, $p<0.0001$ for women) and waist-to-hip ratio ($r=0.19$, $p<0.0001$ for men and $r=0.23$, $p<0.0001$ for women). A linear relationship between the

Table 1. Clinical Characteristics and Laboratory Values of a Random Population of the Northern Persian Gulf (the Study Population)

	Men (n=864)	Women (n=890)	p value
BMI, kg/m^2	26.05 (4.64)	28.39 (5.69)	<0.0001
Systolic blood pressure, mmHg	130.92 (47.47)	121.46 (23.56)	<0.0001
Diastolic blood pressure, mmHg	83.71 (47.58)	77.25 (18.25)	<0.0001
Total cholesterol, mg/dl	201.60 (46.42)	210.27 (48.78)	<0.0001
HDL cholesterol, mg/dl	41.41 (31.34)	48.07 (42.28)	<0.0001
LDL cholesterol, mg/dl	117.36 (63.38)	120.67 (50.49)	<0.226
Triglyceride, mg/dl	81.06 (108.84)	160.83 (95.22)	<0.0001
Fasting blood sugar, mg/dl	91.28 (36.02)	93.20 (44.18)	<0.319
C-reactive protein, mg/l[a]	1.64 (3.58)	2.33 (4.07)	<0.0001
Body fat, %	24.65 (5.75)	34.09 (6.65)	<0.0001
Smoking, %	36.5	21.9	<0.0001
Physical inactivity, %	68.5	73.1	0.001
Chlamydia pneumoniae, seropositive, %	45.7	35.8	<0.0001
Helicobacter pylori seropositive, %	63.2	60.2	0.109
Cytomegalovirus seropositive, %	92.1	94.3	0.045
Herpes simplex type 1 seropositive, %	83.7	88.5	0.003

Values are mean (SD), except for smoking, physical inactivity, body fat, and seropositivity to infectious markers
BMI body mass index
[a] Geometric mean (SD)

increase in the number of pathogens and CRP concentrations was observed (p=0.007). In women, a linear relationship between the increase in the number of pathogens and percentage of BF was also observed (p= 0.002). However, no such relationship could be found for men (p>0.05).

Table 2 shows the results of multiple linear regression analyses for the correlation between percentage of BF and log hs-CRP after controlling for age, cardiovascular risk factors, and infectious burden divided into two, three, and four pathogens in men and women. In multiple regression analyses, hs-CRP showed significant correlations with percentage of BF after controlling for age, sex, cardiovascular risk factors, and infectious burden divided into two, three, and four pathogens [(β=0.24, p<0.0001), (β=0.2 1, p<0.0001), and (β=0.23, p=<0.0001), respectively]. Likewise, log hs-CRP levels were significantly correlated with waist circumference and waist-to-hip ratio after adjustments for age, cardiovascular risk factors, and infectious burden divided into two, three, and four pathogens in both genders (Table 2).

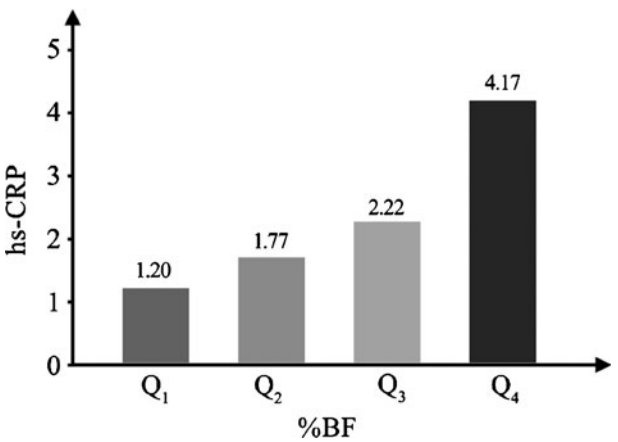

Fig. 1. Geometric mean (SD) of hs-CRP across quartiles of percentage body fat (*%BF*) in men.

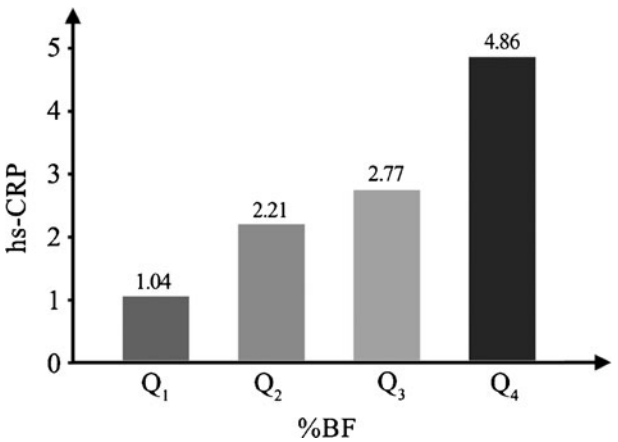

Fig. 2. Geometric mean (SD) of hs-CRP across quartiles of percentage body fat (*%BF*) in women.

Table 2. Multiple Linear Regression Analysis for the Association between Measures of Adiposity (Percentage of Body Fat, Waist-to-hip Ratio, Waist Circumference or Body Mass Index) and hs-CRP levels (dependent variable) in different models

	Men		Women	
	β	p	β	p
Percentage of body fat				
Model 1	0.19	0.007	0.48	<0.0001
Model 2	0.27	<0.0001	0.32	<0.0001
Model 3	0.30	<0.0001	0.42	<0.0001
Waist-to-hip ratio				
Model 1	0.19	0.017	0.26	<0.0001
Model 2	0.16	0.003	0.30	<0.0001
Model 3	0.17	0.013	0.30	<0.0001
Waist circumference				
Model 1	0.20	0.008	0.41	<0.0001
Model 2	0.26	<0.0001	0.43	<0.0001
Model 3	0.25	<0.0001	0.41	<0.0001
Body mass index				
Model 1	0.07	0.314	0.23	<0.0001
Model 2	0.19	<0.0001	0.34	<0.0001
Model 3	0.28	<0.0001	0.37	<0.0001

Model 1 included age, cardiovascular risk factors, and infectious burden divided into two pathogens in addition to percentage of body fat, waist-to-hip ratio, waist circumference or body mass index. Model 2 included percent BF, age, cardiovascular risk factors, and infectious burden divided into three pathogens in addition to percentage of body fat, waist-to-hip ratio, waist circumference, or body mass index. Model 3 included percentage of BF, age, cardiovascular risk factors, and infectious burden divided into four pathogens in addition to percentage of body fat, waist-to-hip ratio, waist circumference, or body mass index

DISCUSSION

In a large representative sample of the Iranian population, we showed a strong correlation between chronic low-grade inflammation and percentage of body fat, independent of the burden of common viral and bacterial pathogens that had been previously associated with coronary artery disease as well as carotid atherosclerosis.

Bioelectrical impedance analysis (BIA), which involves the passage of a weak current across the extremities, is widely accepted as a simple, safe, rapid, low-cost, and reliable technique for determining the percentage of body fat (BF) [26]. Although BMI is a useful index of adiposity, the percentage of BF estimated by BIA may be superior to BMI as a surrogate measure of BF [27]. Hence, more and more attention has been focused on the association between the percentage of BF and coronary artery disease risk factors, metabolic syndrome, and dyslipidemia [26, 28].

In the current study, we found a significant correlation between the percentages of BF measured by BIA and elevated hs-CRP, as a cardiovascular risk in adults. A few studies have used measures of body fat to investigate the association between hs-CRP and obesity [29–32]. In monozygotic twins, CRP concentration was strongly related to both total and central abdominal obesity, independent of genetic influences [29]. In the Insulin Resistance Atherosclerosis Study, measures of body fat were strongly associated with CRP levels [31]. In another population-based study, the percentage of fat mass explained the highest percentage of the variability of CRP in women [30]. Lin *et al*. reported that the percentage of body fat mass was strongly associated with elevated hs-CRP levels in both genders [32].

CRP is produced by hepatocytes, and its gene expression is predominantly regulated by two cytokines, tumor necrosis factor-α and interleukin-6, which are secreted by adipose tissue [33]. The major source of white adipose tissue-produced TNF-α and 50% of white adipose tissue-derived IL-6 are macrophages, which may be attracted to adipose tissue by locally produced proinflammatory cytokines [34]. Therefore, individuals with a higher percentage of body fat may have higher baseline CRP, as we observed in our study. Although adipose tissue may contribute to chronic, low-grade inflammation by triggering the inflammatory cascade, chronic infections with different pathogens also stimulate and amplify the production of proinflammatory cytokines [18]. In our study, a linear relationship between an increase in the number of pathogens and hs-CRP concentrations was also observed. This finding was in accordance with a previous report that showed not only measures of body fat but also pathogen exposure were significant, independent predictors of elevated CRP in Filipino women [35]. Hence, the burden of infection or pathogen exposure may upregulate inflammatory pathways synergistically with adiposity, resulting in elevated CRP concentrations.

On the other hand, Fernandez-Real *et al*. showed a significant association between the burden of infection and fat mass and the percentage of fat mass [19]. They observed a significant linear relationship between the number of infectious pathogens to which an individual has been exposed and the fat mass in healthy middle-aged men [19]. Similarly, an increased prevalence of asymptomatic past *C. pneumoniae* infection in premenopausal obese women with body mass and percentage of BF above median values was reported [18]. In a multinational epidemiological study, seropositivity for

H. pylori and *C. pneumoniae* was both significantly and synergistically associated with overweight [36]. In agreement with those studies, we also found a significant association between the burden of infection and the percentage of BF in women. Thus, the burden of infection or chronic infections with different pathogens could be simultaneously associated with the percentage of body fat and produce chronic low-grade inflammation. For that reason, we investigated the association between percentage of body fat and chronic inflammation with regard to the pathogen burden. In other words, since chronic infections are associated not only with chronic inflammation but also with measures of obesity, adjustment for the burden of infection seems to be essential in logistic regression models when the relationship of chronic inflammation with adiposity is under investigation.

In the current large community-based study, the significant association of the percentage of body fat with circulating levels of hs-CRP persisted when the infectious burden was adjusted for. In other words, the percentage of BF is associated with chronic low-grade inflammation, independent of the burden of common viral and bacterial infections. These results were in agreement with previous results showing that obesity, as measured by the percentage of BF, was a low-grade inflammatory state. Chronic low-grade inflammation (elevated CRP levels) was suggested as a marker of the presence of dysfunctional adipose tissue originating from an obesogenic lifestyle [14]. However, the ultimate reason for increased production of TNF-α and IL-6 by adipose tissue, and the resulting synthesis of CRP by the liver, has not been identified.

Intra-abdominal adipose tissue mass, assessed with computed tomography, showed a significant association with circulating CRP [10, 11]. Waist circumference and WHR have been the traditional anthropometric indices for assessing central obesity. Waist circumference was significantly associated with circulating CRP levels in different studies [10, 37, 38]. Our multivariate analyses demonstrated that waist circumference and WHR also had a significant association with hs-CRP levels, independent of the viral and bacterial infectious burden.

The northern Persian Gulf is classed as a middle-income region from socioeconomic view. However, more than half of men and women aged ≥25 years in this region have unhealthy body weight (BMI>25 or central obesity) [39]. Although more than 86% in rural areas to 100% in urban areas of this region could have access to Primary Health Care Network and a significant improvement in the primary health indices was obtained, we previously reported a high prevalence of unhealthy lifestyle patterns for cardiovascular diseases, metabolic syndrome, and type 2 diabetes among the northern Persian Gulf population [21, 39, 40]. The observed significant discordance between prevalence of chronic diseases and medication consumption in the current study indicates that the overall health system performance in the northern Persian Gulf region is low. Hence, more preventive strategic programs are warranted to combat the epidemic of obesity and other cardiovascular risk factors in this region.

This study has several limitations. First, a causal relationship between chronic low-grade inflammation and adiposity could not be clarified in our cross-sectional study. Second, the use of BIA as an alternative to dual-energy X-ray absorptiometry, which is a newer method for estimating body composition, in overweight and obese populations may have some limitations [41]. Third, since we assessed circulating hs-CRP levels with single measurements, the changes in this acute phase reactant over time could not be reflected in the current study. Furthermore, the measurement of additional inflammatory markers and cytokines merits consideration in order to elucidate the complex system that regulates adipose tissue, the immune system, and inflammation. Fourth, we conducted our study in a large random population and used seropositivity as a marker for infections. Although it has the advantage of clinical applicability, the assessment of infection status based on serology without further clinical or laboratory characterization is subject to diagnostic inaccuracies, especially if seropositivity is common because of the widespread distribution of the incriminated microorganism [42]. In our study, the presence of seropositivity in other confounding viral or bacterial pathogens cannot be ruled out.

In conclusion, there is a strong association between circulating hs-CRP levels and the percentage of BF independent of the viral and bacterial infectious burden in a healthy population. Although it is difficult to conclude whether body fat induces low-grade inflammation or is a consequence of it, a strong association of hs-CRP levels and body fat independent of chronic infections is a promising breakthrough. Furthermore, since chronic low-grade inflammation has been shown to be a predictor of cardiovascular disease, it can be hypothesized that the contribution of body fat to chronic inflammation may be related to the risk of cardiovascular events. Therefore, a reduction in body fat percentage

may prevent the elevation of acute-phase reactants and cytokine levels as well as cardiovascular disease.

ACKNOWLEDGMENTS

This study was supported in part by a grant from Bushehr Province Technology and Research Committee, and Research Deputy of Bushehr University of Medical Science.

REFERENCES

1. Fantuzzi, G. 2005. Adipose tissue, adipokines, and inflammation. *The Journal of Allergy and Clinical Immunology* 115: 911–919.
2. Després, J.P. 2006. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. *European Heart Journal Supplements* 8: B4–B12.
3. Kim, K., R.J. Valentine, Y. Shin, and K. Gong. 2008. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. *Metabolism* 57: 1181–1189.
4. Jialal, I., S. Devaraj, and S.K. Venugopal. 2004. C-reactive protein: risk marker or mediator in atherothrombosis? *Hypertension* 44: 6–11.
5. Pearson, T.A., G.A. Mensah, R.W. Alexander, J.L. Anderson, R.O. Cannon 3rd, M. Criqui, Centers for Disease Control and Prevention, American Heart Association, *et al.* 2003. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107: 499–511.
6. Ford, E.S. 1999. Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22: 1971–1977.
7. Hak, A.E., C.D. Stehouwer, M.L. Bots, K.H. Polderman, C.G. Schalkwijk, I.C. Westendorp, *et al.* 1999. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. *Arteriosclerosis, Thrombosis, and Vascular Biology* 19: 1986–1991.
8. Heilbronn, L.K., and P.M. Clifton. 2002. C-reactive protein and coronary artery disease: influence of obesity, caloric restriction and weight loss. *The Journal of Nutritional Biochemistry* 13: 316–321.
9. Ziccardi, P., F. Nappo, G. Giugliano, K. Esposito, R. Marfella, M. Cioffi, *et al.* 2002. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 105: 804–809.
10. Forouhi, N.G., N. Sattar, and P.M. McKeigue. 2001. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *International Journal of Obesity and Related Metabolic Disorders* 25: 1327–1331.
11. Lemieux, I., A. Pascot, D. Prud'homme, N. Alméras, P. Bogaty, A. Nadeau, *et al.* 2001. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology* 21: 961–967.
12. Pou, K.M., J.M. Massaro, U. Hoffmann, R.S. Vasan, P. Maurovich-Horvat, M.G. Larson, *et al.* 2007. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation* 116: 1234–1241.
13. Faber, D.R., Y. van der Graaf, J. Westerink, and F.L.J. Visseren. 2010. Increased visceral adipose tissue mass is associated with increased C-reactive protein in patients with manifest vascular diseases. *Atherosclerosis* 212: 274–280.
14. Despres, J.P. 2011. CRP: star trekking the galaxy of risk markers. *Lancet* 377: 441–442.
15. Ebrahimi, A., I. Nabipour, K. Vahdat, S.M. Jafari, M. Fouladvand, M. Assadi, *et al.* 2009. High sensitivity C-reactive protein is associated with the metabolic syndrome independent to viral and bacterial pathogen burden. *Diabetes Research and Clinical Practice* 84: 296–302.
16. Zhu, J., A.A. Quyyumi, J.E. Norman, G. Csako, M.A. Waclawiw, G.M. Shearer, *et al.* 2000. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. *The American Journal of Cardiology* 85: 140–146.
17. Adiloglu, A.K., R. Can, C. Nazli, A. Ocal, O. Ergene, G. Tinaz, *et al.* 2005. Ectasia and severe atherosclerosis: relationships with *Chlamydia pneumoniae*, *Helicobacter pylori*, and inflammatory markers. *Texas Heart Institute Journal* 32: 21–27.
18. Koziołek, M., B. Krzyżanowska-Świniarska, I. Mączyńska, T. Miazgowski, and S. Giedrys-Kalemba. 2008. The association between past The association between past *Chlamydia pneumoniae* infection and markers of chronic inflammation in obese women. *European Journal of Clinical Microbiology and Infectious Diseases* 27: 415–421.
19. Fernandez-Real, J.M., M.J. Ferri, J. Vendrell, and W. Ricart. 2007. Burden of infection and fat mass in healthy middle-aged men. *Obesity (Silver Spring)* 15: 245–252.
20. Epstein, S.E., Y.F. Zhou, and J. Zhu. 1999. Infection and atherosclerosis: emerging mechanistic paradigms. *Circulation* 100: e20–e28.
21. Nabipour, I., K. Vahdat, S.M. Jafari, S. Beigi, M. Assadi, F. Azizi, *et al.* 2008. Elevated high sensitivity C-reactive protein is associated with type 2 diabetes mellitus: the Persian Gulf Healthy Heart Study. *Endocrine Journal* 55: 717–722.
22. Lukaski, H.C., P.E. Johnson, W.W. Bolonchuk, and G.I. Lykken. 1985. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. *American Journal of Clinical Nutrition* 41: 810–817.
23. Lintsi, M., H. Kaarma, and I. Kull. 2004. Comparison of hand-to-hand bioimpedance and anthropometry equations versus dual-energy X-ray absorptiometry for the assessment of body fat percentage in 17–18-year-old conscripts. *Clinical Physiology and Functional Imaging* 24: 85–90.
24. 1997. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20:1183–1197.
25. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. 2001. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *The Journal of the American Medical Association* 285: 2486–2497.
26. Kobayashi, J., S. Murano, I. Kawamura, F. Nakamura, Y. Murase, M.A. Kawashiri, *et al.* 2006. The relationship of percent body fat by bioelectrical impedance analysis with blood pressure, and glucose and lipid parameters. *Journal of Atherosclerosis and Thrombosis* 13: 221–226.
27. Roubenoff, R., G.E. Dallal, and P.W. Wilson. 1995. Predicting body fatness: the body mass index vs estimation by bioelectrical impedance. *American Journal of Public Health* 85: 726–728.
28. Zhu, S., Z. Wang, W. Shen, S.B. Heymsfield, and S. Heshka. 2003. Percentage body fat ranges associated with metabolic syndrome risk: results based on the third National Health and Nutrition Examination Survey (1988–1994). *American Journal of Clinical Nutrition* 78: 228–235.

29. Greenfield, J.R., K. Samaras, A.B. Jenkins, P.J. Kelly, T.D. Spector, J.R. Gallimore, *et al.* 2004. Obesity is an important determinant of baseline serum C-reactive protein concentration in monozygotic twins, independent of genetic influences. *Circulation* 109: 3022–3028.
30. Thorand, B., J. Baumert, A. Doring, C. Herder, H. Kolb, W. Rathmann, *et al.* 2006. Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis* 184: 216–224.
31. Festa, A., R. D'Agostino Jr., K. Williams, A.J. Karter, E.J. Mayer-Davis, R.P. Tracy, *et al.* 2001. The relation of body fat mass and distribution to markers of chronic inflammation. *International Journal of Obesity and Related Metabolic Disorders* 25: 1407–1415.
32. Lin, C.C., S.L. Kardia, C.I. Li, C.S. Liu, M.M. Lai, W.Y. Lin, *et al.* 2010. The relationship of high sensitivity C-reactive protein to percent body fat mass, body mass index, waist-to-hip ratio, and waist circumference in a Taiwanese population. *BMC Public Health* 10: 579.
33. Trayhurn, P., and J.H. Beattie. 2001. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proceedings of the Nutrition Society* 60: 329–339.
34. Weisberg, S.P., D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, and A.W. Ferrante Jr. 2003. Obesity is associated with macrophage accumulation in adipose tissue. *The Journal of Clinical Investigation* 112: 1796–1808.
35. McDade, T.W., J.N. Rutherford, L. Adair, and C. Kuzawa. 2008. Adiposity and pathogen exposure predict C-reactive protein in Filipino women. *Journal of Nutrition* 138: 2442–2447.
36. Thjodleifsson, B., I. Olafsson, D. Gislason, T. Gislason, R. Jogi, and C. Janson. 2008. Infections and obesity: a multinational epidemiological study. *Scandinavian Journal of Infectious Diseases* 40: 381–386.
37. Pannacciulli, N., F.P. Cantatore, A. Minenna, *et al.* 2001. C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *International Journal of Obesity and Related Metabolic Disorders* 25: 1416–1420.
38. Park, H.S., J.Y. Park, and R. Yu. 2005. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Research and Clinical Practice* 69: 29–35.
39. Nabipour, I., M. Amiri, S.R. Imami, S.M. Jahfari, A. Nosrati, D. Iranpour, *et al.* 2008. Unhealthy lifestyles and ischaemic electrocardiographic abnormalities: the Persian Gulf Healthy Heart Study. *Eastern Mediterranean Health Journal* 14: 858–868.
40. Nabipour, I., M. Amiri, S.R. Imami, S.M. Jahfari, E. Shafeiae, A. Nosrati, *et al.* 2007. The metabolic syndrome and nonfatal ischemic heart disease; a population-based study. *International Journal of Cardiology* 118: 48–53.
41. Pateyjohns, I.R., G.D. Brinkworth, J.D. Buckley, M. Noakes, and P.M. Clifton. 2006. Comparison of three bioelectrical impedance methods with DXA in overweight and obese men. *Obesity (Silver Spring)* 14: 2064–2070.
42. Nabipour, I., K. Vahdat, S.M. Jafari, R. Pazoki, and Z. Sanjdideh. 2006. The association of metabolic syndrome and *Chlamydia pneumoniae*, *Helicobacter pylori*, cytomegalovirus, and herpes simplex virus type 1: the Persian Gulf Healthy Heart Study. *Cardiovascular Diabetology* 5: 25.